REMARKS

Status of the claims

With entry of the instant amendment, claims 22-26 and 30-32 have been cancelled and new claims 57-72 have been added. Claims 1-4, 7-11, 13, 14, 16, 17, and 50-72 are therefore pending and under examination.

The amendments to the claims add no new matter.

Claims 8, 9, 16, and 54 have been amended to correct dependency.

Claim 56 has been amended to comport with the language in claim 50.

New claims 57, 58, 59, 60, 61, 62, 63, 64, and 65 correspond to cancelled claims 22, 23, 26, 29, 30, 31, 32, 24, and 25, respectively.

New claims 66, 67, 68, and 69 recite a malignant B cell that is a chronic lymphocytic leukemia cell, a hairy cell leukemia cell, a prolymphocytic leukemia cell, and a B cell lymphoma cell, respectively. Support can be found, *e.g.*, in the specification at page 48, lines 1-14; and page 14, lines 15-18.

New claims 70-72 recite pharmaceutical compositions. Support can be found, *e.g.*, in the section beginning on page 27.

The rejection are addressed in the order set forth in the Office Action mailed October 18, 2005.

Rejection under 35 U.S.C. § 112, enablement

The Examiner maintained the rejection of claims 50 and 56 as allegedly not enabled. Applicants respectfully traverse. The rejection is based on the reasoning that the specification is not enabled for any amino acid sequence that is 95% identical to the CDRs of SEQ ID NOs:2 and 4 because of the alleged unpredictability in altering CDRs. However, the claims do not recite a sequence that is 95% identical to the CDRs of SEQ ID NO:2. The claims recite that the V_H and V_L regions have the CDRs of SEQ ID NOs. 2 and 4 and have the recited percent identity to SEQ ID NOs. 2 and 4. Thus, there are two elements of the claimed sequences. The claims clearly state these two elements. Accordingly, the Examiner's argument

that one of skill in the art could not predict that an antibody that has 95% identity to SEQ ID NO:2 or 4 with alterations in the CDRs would have the required binding specificity is not applicable to the instant claims. Applicants therefore respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 103

The rejection of the claims as allegedly obvious was maintained. This rejection is traversed. The Examiner has not established a proper case of *prima facie* obviousness for reasons of record. Even assuming *arguendo* that such a case had been made, the claimed compositions are patentable due to the surprisingly superior properties of the claimed compositions, as explained in Applicants' previous responses. Further, the current claims are patentable over the cited art for the additional reasons provided below.

The claimed compositions and methods are directed to the treatment of B-cell malignancies, *e.g.,* B-cell lymphoma, hairy cell leukemia and chronic lymphocytic leukemia. The Examiner contends that one of skill would have been motivated to make the claimed RFB4-dsFv conjugates and that they would be expected to work because of the teachings in the prior art. The Examiner additionally alleges that the superior binding properties and cytotoxicity exhibited by the claimed conjugates would be expected based on the teachings in the art. Specifically, the Examiner argues that Reiter *et al.* (*Biochemistry*) clearly show better cytotoxicity for dsFv-toxin conjugates as compared to scFv conjugates as well as better expression yields and better stability. The Examiner further characterizes Reiter *et al.* as teaching that scFv molecules can retain the specificity and affinity of IgG, referring to page 5451. First, Applicants disagree with the Examiner's characterization of this reference. The passage referred to by the Examiner states that "[s]uch single-chain Fv's (scFv's) can retain specificity and affinity...." . This merely states that scFv's retain affinity, it does not teach that the affinity is equivalent to that of the parent Ig molecule. In addition, the reference provides no teaching or suggestion that a toxin-dsFv conjugate can retain the binding affinity of a parent IgG.

Next, the Examiner alleges that Shen *et al.* teach that the Fab'-RFB4 bound 1.2 to 3.5 times stronger than other Fab' fragments and that this demonstrates that the art recognized the superior binding affinity of RFB4. However, Shen *et al.* teach that the Fab' fragment for RFB4 had a lower binding affinity relative to the intact antibody. Furthermore, Shen *et al.* show that the Fab' molecules when conjugated to a toxin moiety, the ricin A chain, do not retain the affinity of the parent RFB4 antibody (see, Table 1, page 793 comparing the affinity constant of the IgG, the Fab' and the Fab'-A.). Thus, prior art RFB4 immunotoxin compounds do not exhibit the particular benefit of the currently claimed compositions.

The Examiner further contends that Reiter *et al.* (*Nature Biotechnology*) teach that four out of eight dsFv immunotoxins have improved binding affinity and that the surprising binding properties of the RFB4-dsFv can therefore be expected. However, this comparison appears to be based on a comparison of dsFv-toxin to scFv-toxin. Reiter *et al.* in fact show that it is uncommon that the dsFv toxin conjugate molecules retain the binding affinity of the parent IgG molecules (see, Table 2, page 1242). The Declaration under 37 C.F.R. § 1.132 by Dr. Fitzgerald filed March 11, 2004 further attests that such a result is unexpected. In view of the specific teaching in the prior art that an RFB4(Fab')-toxin conjugate does not retain binding affinity equivalent to the parent immunoglobulin and the knowledge that it is generally uncommon that a immunotoxin conjugate would do so, Applicants assertion of unexpected and superior results of the claimed compositions is proper.

Again assuming *arguendo* that a proper case of *prima facie* obviousness had been presented in the rejection, the claimed compositions have additionally been demonstrated to have surprisingly superior cytotoxic properties in humans *in vivo*. The Declaration by Dr. Fitzgerald, *supra*, points to the cytoxocity of RFB4dsFv-PE38 in Phase I clinical trials for the treatment of patients with a B cell malignancy as further evidence of the superior potency of the claimed compositions. The Examiner has provided no evidence that this degree of efficacy (of sixteen patients in the trial, 11 patients achieved complete remission and 2 patient achieved partial remission; see, Dr. Fitzgerald's Rule 1.132 Declaration filed May 15, 2001) could have been expected from the prior art.

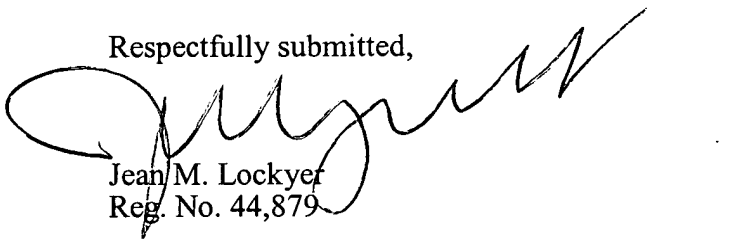
In view of the foregoing, the claims are patentable over the cited art. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Jean M. Lockyer
Reg. No. 44,879

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
JML:jml
60698354 v1